Liver Transplantation: From Inception to Clinical Practice

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The 2012 Lasker-DeBakey Clinical Medical Research Award will be conferred on Thomas Starzl of the University of Pittsburgh School of Medicine in Pittsburgh, Pennsylvania, USA and Roy Calne of the University of Cambridge in Cambridge, UK. They are recognized for pioneering the development of liver transplantation, an intervention that saves 20,000 lives world-wide each year.

A Multitalented Organ

The liver is the largest solid organ in the human body and performs a remarkably diverse array of functions that are essential for survival. It is the source of the vast majority of abundant plasma proteins, including blood clotting factors, albumin, and other proteins that carry a variety of lipophilic hormones in the plasma, lipoproteins that transport cholesterol and triglycerides, and transferrin, which carries iron in the ferric form (Fe^{3+}). The liver also plays a critical role in energy homeostasis, receiving nearly all of the venous blood drainage from the intestines, thereby being the first site receiving ingested nutrients and playing a major role in both storing absorbed carbohydrates in the form of glycogen when energy balance is positive and sustaining blood glucose levels via gluconeogenesis when plasma glucose levels are low. The liver is also responsible for clearing or detoxifying diverse molecules absorbed from the gut, such as bacterial lipopolysaccharide (LPS), and for metabolizing for elimination products of catabolism in the systemic circulation.

As a result of these diverse and vital functions, it is not surprising that acute loss of liver function can lead to death within days, with profuse hemorrhage, profound hypotension, hypoglycemia, and encephalopathy. Chronic liver damage ultimately produces a similar set of problems but has the additional complication that the normal liver architecture is lost and replaced by fibrotic tissue (called cirrhosis), requiring blood to bypass the liver and resulting in dramatic shunting of blood through vessels poorly suited to carrying such large blood volumes. These dilated vessels, called varices, are prone to potentially fatal rupture. In addition, the increased resistance to blood flow through the liver leads to fluid accumulation in the peritoneum (called ascites), which frequently becomes infected. Nonetheless, because there is considerable hepatic reserve and also remarkable capacity of the liver to regenerate after injury, many insults that cause damage to the liver do not cause clinical signs or symptoms, and these typically only appear when less than 10% of normal liver function remains.

The causes of liver failure are diverse (Table 1), and understanding its etiology has led to substantial progress in prevention of liver failure, particularly among infectious causes. Identification of the Hepatitis B virus led to the virtual elimination of transmission by blood transfusion and to development of an efficacious vaccine. The Nobel Prize in Medicine was awarded in 1976 to Baruch Blumberg for the discovery of viral antigens that initiated these developments. More recently, identification of the Hepatitis C virus has been followed by development of new effective therapeutic regimens that can eliminate this virus in a large fraction of affected subjects (Jacobson et al., 2011; Poordad et al., 2011). Despite these advances, more than 700,000 people die annually from liver failure, representing a leading cause of global death.

Toward Transplantation

Unlike kidney failure, for which dialysis can provide long-term replacement of normal kidney function, respiratory failure, which can be overcome by supplemental oxygen and ventilation, and heart failure, which has a variety of pharmacologic and mechanical assist devices that can augment normal function, because of the high diversity of liver functions, there is presently no long-term "liver replacement" therapy. As a consequence, liver transplantation was recognized as a potential therapy, with work beginning in the 1950s. At that time, progress was being made in both bone marrow and kidney transplantation. The first successful human kidney transplant had been performed by Murray in 1954 at Brigham and Women's Hospital, and bone marrow transplantation was achieved by Thomas in 1956 at the Fred Hutchinson Cancer Center. Murray and Thomas shared the Nobel Prize in Medicine in 1990 for these achievements. Efforts in orthotopic liver transplantation began in parallel. Attempted liver transplantation in dogs was reported by Staudacher in 1952, Welch in 1955, and Cannon in 1957 but encountered numerous obstacles, including preservation of the harvested liver prior to transplantation, management of the anhepatic state in the recipient, and challenges to the surgical connection of the transplanted liver to its dual blood supplies, venous drainage, and biliary system (Figure 1). These early efforts produced only short-term survival.

In addition to these hurdles, it was recognized that immune rejection of transplanted organs was a major complicating factor; for this reason, Thomas and Murray both did their initial transplants

Table 1. Causes of Liver Failure Leading to Transplantation
Infectious Diseases
Hepatitis B virus
Hepatitis C virus
Nonviral Hepatic Inflammation
Nonalcoholic steatohepatitis
Autoimmune hepatitis
Primary sclerosing cholangitis
Primary biliary cirrhosis
Chemical/Drug Exposure
Ethanol
Acetaminophen
Other medications: antibiotics, anticonvulsants, NSAIDs
Amatoxins from Amanita phalloides mushroom
Herbal supplements: kava, ephedra, skullcap, and pennyroyal
Industrial toxins: carbon tetrachloride, vinyl chloride
Congenital Abnormalities/Genetic Diseases
Biliary atresia
Alagille syndrome
Alpha-1-antitrypsin deficiency
Wilson's disease
Hereditary hemochromatosis
Tyrosinemia
Homozygous familial hypercholesterolemia
Glycogen storage diseases (Types I, IV)
Cancer
Hepatocellular carcinoma
Cholangiocarcinoma
Hepatoblastoma

between identical twins. These considerations led to recognition that minimizing the immune response to allografts would be critical for transplantation to advance in clinical practice. The discovery of the antigens of the major histocompatibility complex and their important role in transplant rejection led to development of methods for determining human leucocyte antigen (HLA) types and matching for major histocompatibility antigens. This succeeded in reducing, but not eliminating, rejection of transplanted organs. Interestingly, the liver ultimately proved more tolerant of antigenic mismatch than most other tissues, requiring only matching of ABO blood type. Rejection nonetheless remained a major obstacle, which led to recognition that pharmacologic inhibition of the immune response would be an essential component of transplantation.

Impact of Immunosuppression

Roy Calne, a surgeon at University of Cambridge, made major contributions to the development of effective clinical regimens for immunosuppression. In 1951, Elion and Hitchings at Burroughs Wellcome, who received the Nobel Prize in Medicine in 1988, developed an inhibitor of purine biosynthesis, 6-mercaptopurine (6-MP), which proved to have potent activity in the treatment of childhood leukemia. Based on this observation, Robert Schwartz at Tufts Medical School in Boston subsequently demonstrated the ability of 6-MP to reduce the immune response. Calne picked up on these leads and showed that 6-MP and subsequently azathioprine, a prodrug also developed by Elion and Hitchings, had the ability to inhibit rejection of autologous kidney transplants in dogs (Calne, 1960, 1961). These developments had broad impact, leading to effective regimens for transplant of human kidneys among nonidentical twins, achieved in 1962, and also to the first reports of extended survival with liver transplant in dogs, reported in 1960 by Moore and colleagues at Brigham and Women's Hospital in Boston and Starzl and colleagues at University of Colorado in Denver (Moore et al., 1960; Starlz et al., 1960).

Spurred by these successes, on March 1, 1963, Starzl and colleagues performed the first human liver transplant in a child with congenital biliary atresia and followed this effort by two further transplants in adult patients in May and June of the same year (Starzl et al., 1963). Immunosuppression with azathioprine was used in each case, with various adjunctive interventions, including thymectomy, prednisone, and/or splenectomy. The first patient died in surgery due to uncontrollable hemorrhage, whereas the latter two died from pulmonary embolism within days of surgery. Similar failures elsewhere curtailed efforts for several years until improvements in surgical techniques, donor organ procurement and preservation, and immunosuppressive regimens were developed.

It was only in 1967 that Starzl performed the first liver transplant that resulted in survival of the recipient for more than 12 months (Starzl et al., 1968). Shortly thereafter, Calne and colleagues performed the first liver transplant in Europe (Calne and Williams, 1968). In the years following, these two teams pioneered and perfected the techniques of liver transplantation. This entailed painstaking efforts that often resulted in incremental improvements in harvesting and preservation of cadaveric donor livers, surgical techniques of removal of the diseased liver in patients with abnormal vascularization patterns secondary to portal hypertension and severe clotting factor deficiency, and technical improvements in reconstruction of the biliary tract associated with the insertion of the transplanted liver. Collectively, these advances still achieved relatively low 1 year survival rates. Among 170 liver transplants between 1967 and 1980, Starzl's team reported only a 30% 1 year survival rate (Starzl et al., 1982). Calne's series of 130 liver transplants between 1968 and 1983 achieved similar results (Rolles et al., 1984). It was apparent that acute and chronic rejection of the donor liver by the host immune system remained a major clinical problem that was limiting the efficacy of liver transplantation.

From Experimental Treatment to Widespread Use

The last critical advance that ultimately changed the course of liver transplantation came with the development of a new immunosuppressant, cyclosporine A, which was discovered in 1972 at Sandoz. Cyclosporine A is a calcineurin inhibitor that decreases interleukin 2 (IL-2) production and significantly suppresses effector T cell function and associated cytokine release. Calne and others obtained extremely encouraging experimental results using this new compound in animal organ grafts, which was followed shortly by introduction into human transplantation (Calne et al., 1978, 1979). Three years later, Starzl reported a doubling of the 1 year survival rate of liver transplant recipients to about 60% using cyclosporine and prednisone for immunosuppression after liver transplantation (Starzl et al., 1981).

Armed with these marked improvements in survival, and with FDA approval of cyclosporine for immunosuppression

for solid organ transplantation, a consensus meeting on liver transplantation was convened by the National Institutes of Health of the USA in 1983, which concluded that this surgical procedure was no longer experimental but was a therapeutic option for liver failure that was destined to result in death. With this logjam broken, liver transplantation came into the clinical armamentarium and began being performed on a much larger scale by far more surgeons, many of whom were trained by Starzl and Calne.

From this beginning, liver transplantation has been established as a life-saving treatment for liver failure. It is estimated that 20,000 people receive liver transplants each year world-wide in several hundred centers (WHO, 2008). Between January 1, 1988 and April 30, 2012, 115,458 liver transplants were performed in the USA alone. The 1 year survival of a liver transplant patient has improved to 85%–88%, and the 5 year survival is ~74% (The U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients, 1997–2007, http://optn.transplant.hrsa.gov/).

Improvements in liver transplantation have continued. In 1994, tacrolimus (FK506, also a calcineurin inhibitor) was approved by the FDA for use in liver transplantation and then extended to other organ transplantations. Randomized clinical trials have shown superiority of tacrolimus over cyclosporine in preventing rejection and graft loss. Current approaches commonly employ immunosuppression early after transplantation with tacrolimus and glucocorticoids, followed by tapering of steroid dosage in the first 6 months posttransplantation. Beyond this period, the immunosuppressive regimen is reduced to the minimal doses required to prevent chronic rejection, thereby minimizing the risk of adverse effects. A number of new immunosuppressive drugs have been introduced, such as sirolimus (inhibitor of mammalian target of rapamycin [mTOR]), mycophenolate mofetil (inhibitor of purine synthesis), IL-2-receptor-blocking antibody, and anti-CD3 monoclonal antibody, which allow customization of the immunosuppression regimen. Additionally, improved medical management of patients prior to and after transplantation, including new drugs for infectious complications in transplant recipients, has also contributed to improved survival.

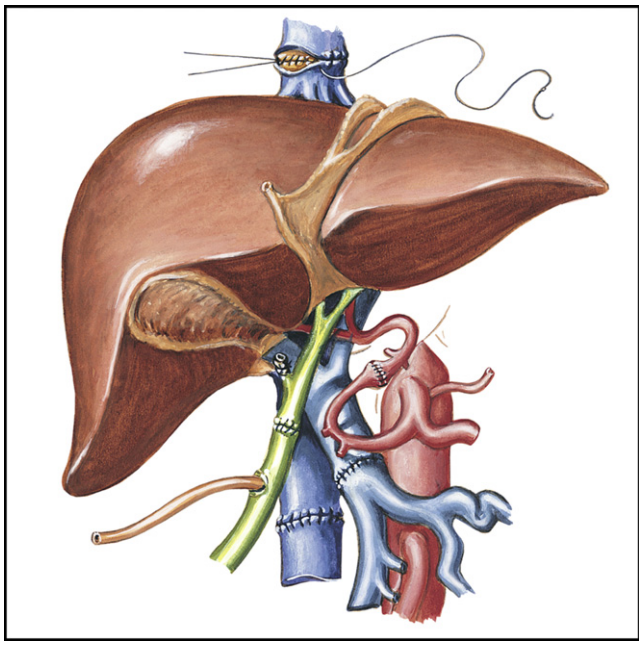

Figure 1. Orthotopic Liver Transplantation
The donor liver is shown in place after transplantation into the recipient. Anastomoses occur between the native and donor hepatic artery (red), portal vein (blue), inferior vena cava (blue), and common bile duct (green).

A Problem of Scarcity

Despite the striking success of liver transplantation, its application remains limited by organ availability. Thus, there are more than 16,000 patients listed for liver transplantation in the United States, but only 5,000–6,000 liver transplants are performed each year, and more than 2,000 people die annually while waiting for a liver transplant. This has led to the establishment of rigorous criteria for allocation of donor livers. Patients with end-stage liver disease are typically referred for liver transplantation evaluation at the time of their first decompensation. Patients may be listed for transplantation unless they have comorbidities that make survival after transplantation unlikely. These include advanced cardiopulmonary disease, incurable extrahepatic malignancy, and active alcohol or substance abuse. Among patients listed for transplant who are an ABO blood type match to the donor organ, priority is given to patients with the shortest expected survival without transplantation, based on objective biochemical measures of liver and kidney function. Matching of body size and vascular anatomy of donor and recipient are also critical in final organ allocation.

The scarcity of donor organs has prompted efforts to develop living donor liver transplantation (LDLT), taking advantage of the liver's regenerative capacity. The first successful LDLT was performed in 1989 by Broelsch and colleagues in a child with biliary atresia at the University of Chicago. Living donation of the lateral segment of the left lobe of the liver has become an accepted practice in pediatric transplantation, with excellent donor and recipient outcomes. The relatively small mass of the left hepatic lobe, however, has limited the utility of left lobe transplantation in adult recipients.

Recognizing limitations inherent to transplantation, efforts continue to develop artificial extracorporeal liver support. The Molecular Adsorbents Recirculating System (MARS), developed at the University of Rostock in Germany and clinically available since 2005, consists of two separate dialysis circuits that are capable of removing a number of lipophilic, albumin-bound toxins, including ammonia, bile acids, and bilirubin. Though only of short-term utility, this system can be used in cases of acute liver failure as a bridge to transplantation.

Perspective

The work of Starzl and Calne in bringing liver transplantation from inception to a widely used life-saving procedure

represents a spectacular achievement realized despite daunting obstacles and years of failure in human experimentation that offered scant promise of long-term success. Their ultimate achievement required remarkable innovation and courage, melding surgical technique, the basic science and pharmacology of the immune system, and masterful management of the highly complex and dynamic physiology that results from liver failure and its correction via transplantation. The scientific underpinnings of all of the elements involved in completion of a successful liver transplant are truly staggering in their scope. In addition to their innovating spirit, it is worth contemplating the breadth of basic and clinical disciplines that Starzl and Calne had to command in order to bring liver transplantation to practice. The resulting benefit to patients provides a compelling argument for the broad training of physicians in basic and clinical disciplines and for continued—and patient—support for innovative work to advance human health.

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